Sci. Vol. 66, 2009; and Arthur M. Mandelin II, Richard M. Pope, Expert Opin. Ther. Targets (2007) 11(3):363-373.

New compositions and methods for preparing and formulating Mcl-1 inhibitors would be useful.

BRIEF DESCRIPTION OF DRAWINGS

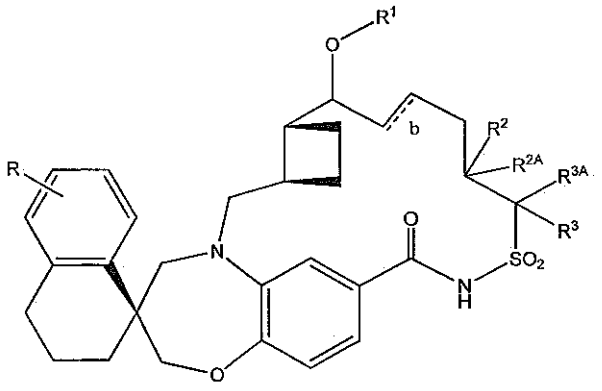
Figure 1 illustrates the Mcl-1 inhibitor *in-vivo* efficacy of the compound of Example 4.

Figure 2 illustrates the Mcl-1 inhibitor in-vivo efficacy of the compound of Example 17.

Figure 3 illustrates the Mcl-1 inhibitor in-vivo efficacy of the compound of Example 20.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides compounds of Formula I,



(I)

wherein, b, represented by the symbol ------ is a single or double chemical bond which may be cis or trans; R is a halogen; R^1 is H, C_1-$_6$alkyl, and $(CH_2CH_2O)_nCH_3$, wherein n is an integer from 1 to 4; R^2 is H or C_1-$_6$alkyl; R^{2A} is H or C_1-$_6$alkyl; R^3 is H or C_1-$_6$ alkyl; and R^{3A} is H, C_1-$_6$ alkyl, C_3-$_6$ cycloalkyl, or $(CH_2)_m$-C_3-$_6$ cycloalkyl, wherein m is an integer from 1 to 4. In one embodiment, R is Cl. In one embodiment, R^1 is C_1-$_6$ alkyl. In another embodiment, R^1 is CH_3. In one embodiment, R^2 is H and R^{2A} is C_1-$_6$ alkyl. In one embodiment, R^3 is H and R^{3A} is C_1-$_6$ alkyl. In another embodiment, b indicates a double bond.

One embodiment of the present invention is directed to a pharmaceutical composition comprising the compound of Formula I, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In one aspect, the present invention refers to the use of the compound of the present invention in the manufacture of a medicament for treating cancer, wherein the cancer is a hematologic malignancy and further wherein the medicament is to be administered to the subject orally, parenterally, via injection, via inhalation, transdermal, or transmucosal in a subject. In still another aspect, the present invention refers to the use of the compound of the present invention, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient in need thereof wherein the cancer is a hematologic malignancy. In one aspect, the present invention is directed to a compound according to the present invention for use in treating cancer in a subject, wherein the cancer is a hematologic malignancy.

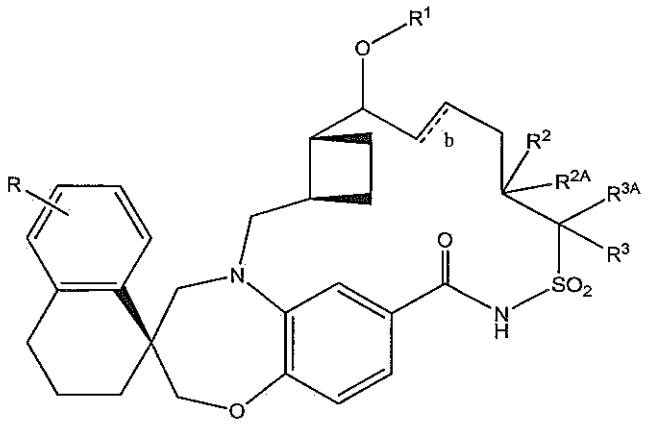
Also described herein is a method of inhibiting myeloid cell leukemia 1 protein (Mcl-1) of a cell comprising contacting the cell with the compound of Formula I in an effective amount to inhibit the Mcl-1, in conjunction with any of the above or below embodiments.. In one example, the contacting is *in vitro*. In another example, the contacting is *in vivo*. In one example, the contacting comprises administering the compound to a subject. In one example, the administering is oral, parenteral, via injection, via inhalation, transdermal, or transmucosal. In one example, the subject suffers from cancer.

One example described herein is directed to a method of the treatment of cancer, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I or a pharmaceutical composition comprising the compound of Formula I, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, in conjunction with any of the above or below embodiments. In one embodiment, the cancer is a hematologic malignancy. In one example, the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's

CLAIMS

What is claimed is:

1. A compound of Formula I:



(I);

or a pharmaceutically acceptable salt thereof,

wherein:

wherein b, represented by the symbol ------ is a single or double chemical bond which may be cis or trans;

R is a halogen;

R^1 is H, C_{1-6} alkyl, or $-(CH_2CH_2O)_nCH_3$, wherein n is an integer from 1 to 4;

R^2 is H or C_{1-6} alkyl;

R^{2A} is H or C_{1-6} alkyl;

R^3 is H or C_{1-6} alkyl; and

R^{3A} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_m$-C_{3-6} cycloalkyl, wherein m is an integer from 1 to 4.

2. The compound of claim 1, wherein b------ indicates a double bond.

3. The compound of claim 1 or claim 2, wherein R is Cl.

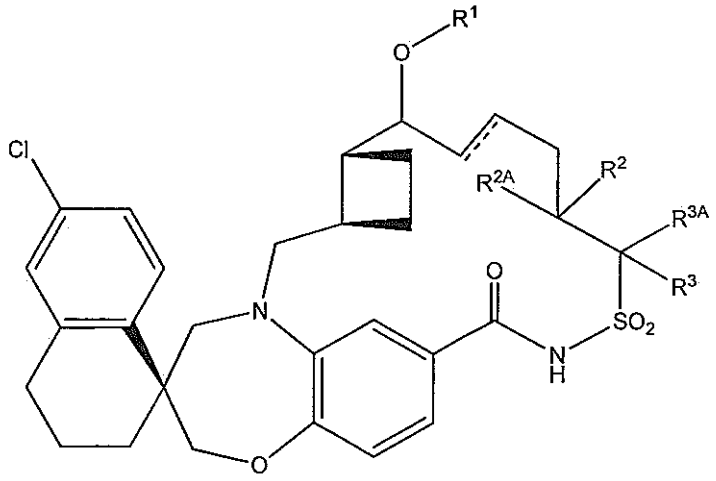
4. The compound of claim 1, wherein R^1 is C_{1-6} alkyl.

5. The compound of claim 4, wherein R^1 is CH_3.

6. The compound of any one of claims 1-5, wherein R^2 is H and R^{2A} is C_{1-6} alkyl.

7. The compound of any one of claims 1-6, wherein R^3 is H and R^{3A} is C_{1-6} alkyl.

8. The compound of claim 1, wherein the compound of Formula I has the Formula II:



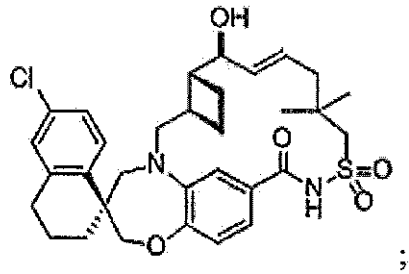
(II)

or a pharmaceutically acceptable salt thereof,

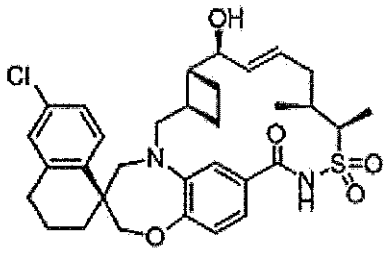
wherein:

R^1, R^2, R^{2A}, R^3 and R^{3A} are defined in claim 1.

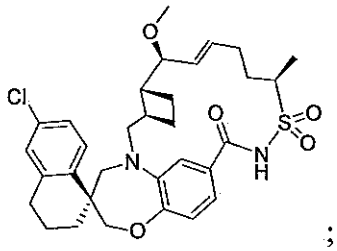
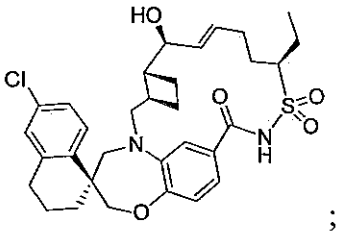
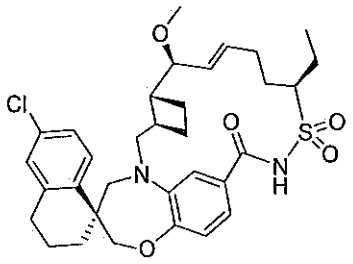
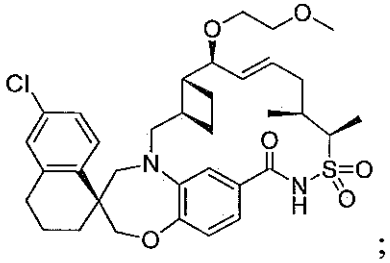
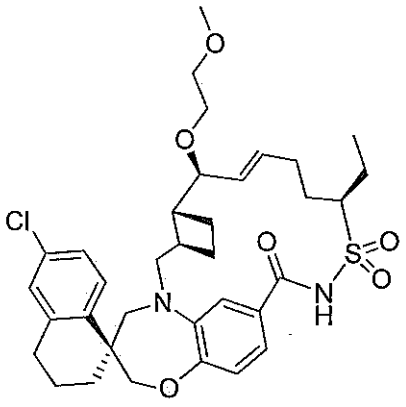
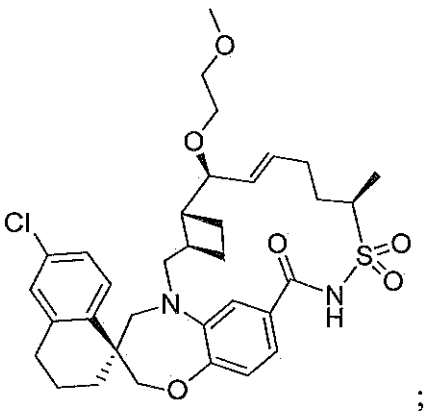
9. A compound, wherein the compound has a structure selected from:



;



;


;

;

;

;

; or

;

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising the compound of claim 11 or the pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

13. Use of the compound of any one of claims 1-9 or 11 in the manufacture of a medicament for treating cancer in a subject, wherein the cancer is a hematologic malignancy and further wherein the medicament is to be administered to the subject orally, parenterally, via injection, via inhalation, transdermal, or transmucosal.

14. The use of claim 13, wherein the cancer is multiple myeloma.

15. Use of the compound of any of claims 1-9 or 11, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein the cancer is a hematologic malignancy.

16. The use of claim 15, wherein the cancer is acute myelogenous leukemia.

17. The use claim 15, wherein the cancer is selected from lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, or acute myelogenous leukemia.

18. The use of claim 15, wherein the cancer is multiple myeloma.

19. The use of claim 15, wherein a therapeutically effective amount of an additional pharmaceutically active compound is to be administered to the patient.

20. The use of claim 19, wherein the additional pharmaceutically active compound is carfilzomib.

21. A compound according to any one of Claims 1-9 or 11 for use in treating cancer in a subject, wherein the cancer is a hematologic malignancy.